SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
MYCOGAB PLUS TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION :
Composition:
Each film coated tablet contains
Gabapentin USP 300 mg
Methylcobalamin 500 mcg
Colour: Ponceau 4R, Titanium dioxide BP
Excipients: q.s.
For full list of Excipients, see section 6.1

3. PHARMACEUTICAL FORM:
Brick red coloured capsule shaped film coated tablet both the sides plain.
Film coated tablet

4. CLINICAL PARTICULARS:
4.1 THERAPEUTIC INDICATIONS
Diabetic neuropathy; trigeminal & post-herpetic neuralgia; back, joint & neck pain; cancer related chemotherapy & radiation induced neuropathic pain; chemotherapy induced hot flashes in breast cancer patients; uremic pruritus; painful neuropathy in chronic renal failure..

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
For all indications a titration scheme for the initiation of therapy is described below, which is recommended for adults and adolescents aged 12 years and above.

Dosing Chart – Initial Titration		
Day 1	Day 2	Day 3
300 mg once a day	300 mg two times a day	300 mg three times a day

Epilepsy typically requires long-term therapy. Dosage is determined by the treating physician according to individual tolerance and efficacy.
In accordance with current clinical practice, if gabapentin has to be discontinued it is recommended this should be done gradually over a minimum of 1 week independent of the indication.
Children aged 6 years and above:
The starting dose should range from 10 to 15 mg/kg/day and the effective dose is reached by upward titration over a period of approximately three days. The effective dose of gabapentin in children aged 6 years and older is 25 to 35 mg/kg/day. Dosages up to 50 mg/kg/day have been well tolerated in a long term clinical study. The total daily dose should be divided in three single doses, the maximum time interval between doses should not exceed 12 hours

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.
Recent myocardial infarction, any degree of heart block or other cardiac arrhythmias.
Severe liver disease.
Mania.

Tobacco amblyopia. Should not be used to treat megaloblastic anaemia of pregnancy. Should not be administered before perncious anaemia or folate deficiency has been ruled out.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Gabapentin

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

Severe, life-threatening, systemic hypersensitivity reactions such as Drug rash with eosinophilia and systemic symptoms (DRESS) have been reported in patients taking antiepileptic drugs including gabapentin.

It is important to note that early manifestations of hypersensitivity, such as fever or lymphadenopathy, may be present even though rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. Gabapentin should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Anaphylaxis

Gabapentin can cause anaphylaxis. Signs and symptoms in reported cases have included difficulty breathing, swelling of the lips, throat, and tongue, and hypotension requiring emergency treatment. Patients should be instructed to discontinue gabapentin and seek immediate medical care should they experience signs or symptoms of anaphylaxis.

Suicidal ideation and behaviour

Suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known. Cases of suicidal ideation and behaviour have been observed in patients treated with gabapentin in the post-marketing experience.

Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge. Patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Discontinuation of gabapentin treatment should be considered in case of suicidal ideation and behaviour.

Acute pancreatitis

If a patient develops acute pancreatitis under treatment with gabapentin, discontinuation of gabapentin should be considered.

Seizures

Although there is no evidence of rebound seizures with gabapentin, abrupt withdrawal of anticonvulsants in epileptic patients may precipitate status epilepticus.

As with other antiepileptic medicinal products, some patients may experience an increase in seizure frequency or the onset of new types of seizures with gabapentin.

As with other anti-epileptics, attempts to withdraw concomitant anti-epileptics in treatment refractive patients on more than one anti-epileptic, in order to reach gabapentin monotherapy have a low success rate.

Gabapentin is not considered effective against primary generalized seizures such as absences and may aggravate these seizures in some patients. Therefore, gabapentin should be used with caution in patients with mixed seizures including absences.

Gabapentin treatment has been associated with dizziness and somnolence, which could increase the occurrence of accidental injury (fall). There have also been post-marketing reports of loss of consciousness, confusion and mental impairment. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medicinal product.

Concomitant use with opioids and other CNS depressants

Patients who require concomitant treatment with central nervous system (CNS) depressants, including opioids should be carefully observed for signs of CNS depression, such as somnolence, sedation and respiratory depression. Patients who use gabapentin and morphine concomitantly may experience increases in gabapentin concentrations. The dose of gabapentin or concomitant treatment with CNS depressants including opioids should be reduced appropriately.
Caution is advised when prescribing gabapentin concomitantly with opioids due to risk of CNS depression. In a reported population-based, observational, nested case-control study of opioid users, co prescription of opioids and gabapentin was associated with an increased risk for opioid-related death compared to opioid prescription use alone (adjusted odds ratio [aOR], 1.49 [95% CI, 1.18 to 1.88, p<0.001]).
Respiratory depression
Gabapentin has been associated with severe respiratory depression. Patients with compromised respiratory function, respiratory or neurological disease, renal impairment, concomitant use of CNS depressants and the elderly might be at higher risk of experiencing this severe adverse reaction. Dose adjustments might be necessary in these patients.
Elderly (over 65 years of age)
No systematic studies in patients 65 years or older have been conducted with gabapentin. In one reported double blind study in patients with neuropathic pain, somnolence, peripheral oedema and asthenia occurred in a somewhat higher percentage in patients aged 65 years or above, than in younger patients. Apart from these findings, clinical investigations in this age group do not indicate an adverse event profile different from that observed in younger patients.
Paediatric population
The effects of long-term (greater than 36 weeks) gabapentin therapy on learning, intelligence, and development in children and adolescents have not been adequately studied. The benefits of prolonged therapy must therefore be weighed against the potential risks of such therapy.
Abuse and Dependence
Cases of abuse and dependence have been reported in the post-marketing database. Carefully evaluate patients for a history of drug abuse and observe them for possible signs of gabapentin abuse e.g. drug-seeking behaviour, dose escalation, development of tolerance.
Laboratory tests
False positive readings may be obtained in the semi-quantitative determination of total urine protein by dipstick tests. It is therefore recommended to verify such a positive dipstick test result by methods based on a different analytical principle such as the Biuret method, turbidimetric or dye-binding methods, or to use these alternative methods from the beginning.
Methylcobalamin:
The prologned use of larger doses of methylcobalamin is not recommended for patients whose occupation requires the handling of mercury or mercury compounds.
Use cautiously in patients with hypertension, cardiovascular and lung diseases. Cardiac arrhythmias secondary to hypokalaemia during initial therapy have been reported. Vitamin B12 should be given prophylactically only when there is a reasonable indication. Administration of methycobalamin doses greater than 10mcg daily, may produce a hematological response in patients with folate deficiency. It is important to monitor methylcobalamin concentrations in plasma and to obtain peripheral blood counts at intervals of 3 to 6 months to confirm that adequacy of therapy. Since refractoriness to therapy can develop at any time, evaluation must continue throughout the patient’s life. Serum concentrations may be decreased by concurrent administration of oral contraceptives. Blood concentrations of methylcobalamin may be reduced if large doses of folate are taken continuously..

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Gabapentin

There are spontaneous and literature case reports of respiratory depression and/or sedation and death associated with gabapentin when co-administered with CNS depressants, including opioids. In some of these reports, the authors considered the combination of gabapentin and opioids to be a particular concern in frail patients, in the elderly, in patients with serious underlying respiratory disease, with polypharmacy, and in those with substance abuse disorders.

In a reported study involving healthy volunteers (N=12), when a 60mg controlled-release morphine capsule was administered 2 hours prior to a 600mg gabapentin capsule, mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Therefore, patients who require concomitant treatment with opioids should be carefully observed for signs of CNS depression, such as somnolence, sedation and respiratory depression and the dose of gabapentin or opioid should be reduced appropriately.

No interaction between gabapentin and phenobarbital, phenytoin, valproic acid, or carbamazepine has been observed.

Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving these antiepileptic agents.

Co-administration of gabapentin with oral contraceptives containing norethindrone and/or ethinyl estradiol, does not influence the steady-state pharmacokinetics of either component.

Co-administration of gabapentin with antacids containing aluminium and magnesium, reduces gabapentin bioavailability up to 24%. It is recommended that gabapentin be taken at the earliest two hours following antacid administration.

Renal excretion of gabapentin is unaltered by probenecid.

A slight decrease in renal excretion of gabapentin that is observed when it is co-administered with cimetidine is not expected to be of clinical importance.

Methylcobalamin:

Tetracycline: Vitamin B12 should not be taken at the same time as the antibiotic Tetracycline because it Interferes with the absorption and effectiveness of this medication. Vitamin B12 either alone or in combinatin with other B vitamins should be taken at different times of the day from tetracycline.

Chemotherapy Medications: Blood levels of Vitamin B12 may be reduced when taking chemotherapy medications (particularly methotrexate) for cancer.

Absorption of cobalamin is impaired by alcohol, vitamin B6 (pyridoxine) deficiency, cholestyramine, para-aminosalicylic acid colchicines, neomycin, the oral bigunades, metformin, histamine H2 receptor antagonists (clmetidine, ranitidine, etc.) phenformin and possibly potassium chloride. A number of anticonvulsants phenobarbitone, primidone, phenytoin, and ethylphenacemide can alter the metabolism of cobalamin in the cerebrospinal fluid and lead to neuropsychotic disturbances. Several substituted amide, lactone and lactum analogues of cyanocobalamin compete with binding sites on intrinsic factor and lead to depressed absorption of the vitamins. Nitrous oxide also interferes with cobalamin metabolism.

4.6 PREGNANCY AND LACTATION

Pregnancy

Risk related to epilepsy and antiepileptic medicinal products in general

The risk of birth defects is increased by a factor of 2 – 3 in the offspring of mothers treated with an antiepileptic medicinal product. Most frequently reported are cleft lip, cardiovascular malformations and neural tube defects. Multiple antiepileptic drug therapy may be associated with a higher risk of congenital malformations than monotherapy, therefore it is important that monotherapy is practiced whenever possible. Specialist advice should be given to women who are likely to become pregnant or who are of childbearing potential and the need for antiepileptic treatment should be reviewed when a woman is planning to become pregnant. No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures, which could have serious consequences for both mother and child. Developmental delay in children of mothers with epilepsy has been observed rarely.
It is not possible to differentiate if the developmental delay is caused by genetic, social factors, maternal epilepsy or the antiepileptic therapy.
Risk related to gabapentin.
Gabapentin crosses the human placenta.
There are no or limited amount of data from the use of gabapentin in pregnant women.
Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Gabapentin should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus.
No definite conclusion can be made as to whether gabapentin is causally associated with an increased risk of congenital malformations when taken during pregnancy, because of epilepsy itself and the presence of concomitant antiepileptic medicinal products during each reported pregnancy.

Breast-feeding

Gabapentin is excreted in human milk. Because the effect on the breast-fed infant is unknown, caution should be exercised when gabapentin is administered to a breast-feeding mother. Gabapentin should be used in breast-feeding mothers only if the benefits clearly outweigh the risks.

Fertility

There is no effect on fertility in animal studies.

4.7 EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES

Gabapentin may have minor or moderate influence on the ability to drive and use machines. Gabapentin acts on the central nervous system and may cause drowsiness, dizziness or other related symptoms.
Even, if they were only of mild or moderate degree, these undesirable effects could be potentially dangerous in patients driving or operating machinery. This is especially true at the beginning of the treatment and after increase in dose..

4.8 UNDESIRABLE EFFECTS

Gabapentin
The adverse reactions observed during clinical studies conducted in epilepsy (adjunctive and monotherapy) and neuropathic pain have been provided in a single list below by class and frequency (very common (> 1/10); common (>1/100, <1/10); uncommon (>1/1000, <1/100); rare (>1/10,000; <1/1,000); very rare (<1/10,000). Where an adverse reaction was seen at different frequencies in clinical studies, it was assigned to the highest frequency reported.
Additional reactions reported from the post-marketing experience are included as frequency 'Not known' (cannot be estimated from the available data) in italics in the list below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	Adverse drug reactions

Infections and infestations	
Very Common	viral infection
Common	pneumonia, respiratory infection, urinary tract infection, infection, otitis media
Blood and the lymphatic system disorders	
Common	leucopenia
Not known	*Thrombocytopenia*
Immune system disorders	
Uncommon	allergic reactions (e.g. urticaria)
Not known	hypersensitivity syndrome (a systemic reaction with a variable presentation that can include fever, rash, hepatitis, lymphadenopathy, eosinophilia, and sometimes other signs and symptoms), anaphylaxis (see section 4.4)
Metabolism and nutrition disorders	
Common	anorexia, increased appetite
Uncommon	hyperglycaemia (most often observed in patients with diabetes)
Rare	hypoglycaemia (most often observed in patients with diabetes)
Not known	hyponatraemia
Psychiatric disorders	
Common	hostility, confusion and emotional lability, depression, anxiety, nervousness, thinking abnormal
Uncommon	agitation
Not known	hallucinations, suicidal ideation
Nervous system disorders	
Very Common	somnolence, dizziness, ataxia
Common	convulsions, hyperkinesias, dysarthria, amnesia, tremor, insomnia, headache, sensations such as paresthesia, hypaesthesia, coordination abnormal, nystagmus, increased, decreased, or absent reflexes
Uncommon	hypokinesia, mental impairment
Rare	loss of consciousness
Not known	other movement disorders (e.g. choreoathetosis, dyskinesia, dystonia)
Eye disorders	
Cardiac disorders	

Uncommon	palpitations
Vascular disorders	
Common	hypertension, vasodilatation
Respiratory, thoracic and mediastinal disorders	
Common	dyspnoea, bronchitis, pharyngitis, cough, rhinitis
Rare	respiratory depression
Gastrointestinal disorders	
Common	vomiting, nausea, dental abnormalities, gingivitis, diarrhoea, abdominal pain, dyspepsia, constipation, dry mouth or throat, flatulence
Uncommon	dysphagia
Not known	pancreatitis
Hepatobiliary disorders	
Not known	hepatitis, jaundice
Skin and subcutaneous tissue disorders	
Common	facial oedema, purpura most often described as bruises resulting from physical trauma, rash, pruritus, acne
Not known	Stevens-Johnson syndrome, angioedema, erythema multiforme, alopecia, drug rash with eosinophilia and systemic symptoms (see section 4.4)
Musculoskeletal and connective tissue disorders	
Common	arthralgia, myalgia, back pain, twitching
Not known	rhabdomyolysis, myoclonus
Renal and urinary disorder	
Not known	acute renal failure, incontinence
Reproductive system and breast disorders	
Common	impotence
Not known	breast hypertrophy, gynaecomastia, sexual dysfunction (including changes in libido, ejaculation disorders and anorgasmia)
General disorders and administration site conditions	
Very Common	fatigue, fever
Common	peripheral oedema, abnormal gait, asthenia, pain, malaise, flu syndrome
Uncommon	generalized oedema

Not known	withdrawal reactions (mostly anxiety, insomnia, nausea, pains, sweating), chest pain. Sudden unexplained deaths have been reported where a causal relationship to treatment with gabapentin has not been established.
Investigations	
Common	WBC (white blood cell count) decreased, weight gain
Uncommon	elevated liver function tests SGOT (AST), SGPT (ALT) and bilirubin
Not known	blood creatine phosphokinase increased
Injury, poisoning and procedural complications	
Common	accidental injury, fracture, abrasion
Uncommon	fall

Under treatment with gabapentin cases of acute pancreatitis were reported. Causality with gabapentin is unclear.
In patients on haemodialysis due to end-stage renal failure, myopathy with elevated creatine kinase levels has been reported.
Respiratory tract infections, otitis media, convulsions and bronchitis were reported only in clinical studies in children.
Additionally, in clinical studies in children, aggressive behaviour and hyperkinesias were reported commonly.
Methylcobalamin:
Generally, well tolerated.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org.

4.9 OVERDOSE
Gabapentin
Acute, life-threatening toxicity has not been observed with gabapentin overdoses of up to 49g. Symptoms of the overdoses included dizziness, double vision, slurred speech, drowsiness, loss of consciousness, lethargy and mild diarrhoea.
All patients recovered fully with supportive care. Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, minimize toxicity from overdoses.
Overdoses of gabapentin, particularly in combination with other CNS depressant medications, may result in coma.
Although gabapentin can be removed by haemodialysis, based on prior experience it is usually not required.
However, in patients with severe renal impairment, haemodialysis may be indicated.

An oral lethal dose of gabapentin was not identified in mice and rats given doses as high as 8000mg/kg.
Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, hypoactivity, or excitation.

Methylcobalamin:

No such case have been described in the literature and it is unlikely that any harm would result.

5. PHARMACOLOGICAL PARTICULARS:

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action:

Gabapentin

Mechanism of action

Gabapentin readily enters the brain and prevents seizures in a number of animal models of epilepsy. Gabapentin does not possess affinity for either GABAA or GABAB receptor nor does it alter the metabolism of GABA. It does not bind to other neurotransmitter receptors of the brain and does not interact with sodium channels. Gabapentin binds with high affinity to the α2δ (alpha-2-delta) subunit of voltage-gated calcium channels and it is proposed that binding to the α2δ subunit may be involved in gabapentin's anti-seizure effects in animals. Broad panel screening does not suggest any other drug targets other than α2δ.

Evidence from several pre-clinical models inform that the pharmacological activity of gabapentin may be mediated via binding to α2δ through a reduction in release of excitatory neurotransmitters in regions of the central nervous system. Such activity may underlie gabapentin's anti-seizure activity. The relevance of these actions of gabapentin to the anticonvulsant effects in humans remains to be established.

Gabapentin also displays efficacy in several pre-clinical animal pain models. Specific binding of gabapentin to the α2δ subunit is proposed to result in several different actions that may be responsible for analgesic activity in animal models. The analgesic activities of gabapentin may occur in the spinal cord as well as at higher brain centres through interactions with descending pain inhibitory pathways. The relevance of these pre-clinical properties to clinical action in humans is unknown.

Methylcobalamin:

Vitamin B12 is necessary for the formation of blood corpuscles, nerve sheaths and various proteins. It is also involved in fat and carbohydrate metabolism and is essential for growth. Adenosylcobalamin is the co enzyme for isomerization of 1-Methylmalonyl Co enzyme A to Succinyl Coenzyme A (an important reaction in lipid and carbohydrate metabolism) and in Ribonucleotide reduction (which provides building blocks for DNA synthesis). Reactions involving methylcobalamin include biosynthesis of methionine, methane and acetate. There is evidence that Vitamin B12 is required the synthesis of folate polyglutamase (active coenzyme required in the formation of nerve tissue) and in the regeneration of folate during red blood cell formation. Methylcobalamin is an endogenous Coenzyme B12 Methylcobalamin plays as important role in transmethylation as a coenzyme of methionine synthetase in the synthesis of methionine from homocystnine.

Gabapentin

Clinical efficacy and safety

A clinical trial of adjunctive treatment of partial seizures in paediatric subjects, ranging in age from 3 to 12 years, showed a numerical but not statistically significant difference in the 50% responder rate in favour of the gabapentin group compared to placebo. Additional post-Page

effect of age, either as a continuous or dichotomous variable (age groups 3-5 and 6-12 years). The data from this additional post-hoc analysis are summarised in the table below: Response (≥ 50% Improved) by Treatment and Age MITT* Population			
Age Category	Placebo	Gabapentin	P-Value
< 6 Years Old	4/21 (19.0%)	4/17 (23.5%)	0.7362
6 to 12 Years Old	17/99 (17.2%)	20/96 (20.8%)	0.5144

*The modified intent to treat population was defined as all patients randomised to study medication who also had evaluable seizure diaries available for 28 days during both the baseline and double-blind phases.

Methylcobalamin:

Methylcobalamin is well transporter to nerve cells organelles and promotes nucleic acid and protein synthesis in animal studies: Methylcobalamin was shown to be better transporter to nerve cell organelles than cyanocobalamin.

It has also been shown in experiments with cells from the brain origin and spinal nerve calls to be involved in the synthesis of thymidine from deoxyuridine, promotion of deposited folate utilization and metabolism of nucleic acid. Also, methylcobalamin plays role in nucleic acid and protein synthesis more than adenosylcobalamin does.

Methylcobalamin promotes axonal transport and axonal regeneration: Methylcobalamin normalizes axonal skeletal protein transport in sciatic nerve cells from rat models with streptozotocin-induced diabetes mellitus. It exhibits neuropathologically and electrophysiologically inhibitory effects on nerve degeneration in neuropathies induced by drugs, such as adriamycin, acrylamide, and vincristine, models of axonal degeneration in mice and neuropathies in rats with spontaneous diabetes mellitus.

Methylcobalamin promotes myelination (phospholipids synthesis): Methylcobalamin promotes the synthesis of lecithin, the main constituent of medullary sheath lipids, and increases myelination of neurons in tissue culture more than adenosylcobalsmin does. Methylcobalamin resotes delayed synaptic transmission and diminished neurotransmitters to normal in animal studies: methylcobalamin restores end-plate potential induction early by addition, methylcobalamin normalizes diminished brain tissue levels of acetyl choline in rats fed a choline dificient diet.

5.2 PHARMACOKINETIC PROPERTIES

Absorption:

Following oral administration, peak plasma gabapentin concentrations are observed within 2 to 3 hours. Gabapentin bioavailability (fraction of dose absorbed) tends to decrease with increasing dose. Absolute bioavailability of a 300mg capsule is approximately 60%. Food, including a high-fat diet, has no clinically significant effect on gabapentin pharmacokinetics.

Gabapentin pharmacokinetics are not affected by repeated administration. Although plasma gabapentin concentrations were generally between 2µg/ml and 20µg/ml in clinical studies, such concentrations were not predictive of safety or efficacy. Pharmacokinetic parameters are given in Table 3.

Summary of gabapentin mean (%CV) steady-state pharmacokinetic parameters following every eight hours administration Pharmacokinetic parameter

Pharmacokinetic parameter	300mg (N = 7)		400mg (N = 14)		800mg (N=14)	
	Mean	%CV	Mean	%CV	Mean	%CV
Cmax (µg/ml)	4.02	(24)	5.74	(38)	8.71	(29)
tmax (hr)	2.7	(18)	2.1	(54)	1.6	(76)
T1/2 (hr)	5.2	(12)	10.8	(89)	10.6	(41)
AUC (0-8) µg•hr/ml)	24.8	(24)	34.5	(34)	51.4	(27)
Ae% (%)	NA	NA	47.2	(25)	34.4	(37)

Cmax = Maximum steady state plasma concentration
tmax = Time for Cmax
T1/2 = Elimination half-life
AUC(0-8) = Steady state area under plasma concentration-time curve from time 0 to 8 hours postdose
Ae% = Percent of dose excreted unchanged into the urine from time 0 to 8 hours postdose
NA = Not available

Distribution:
Gabapentin is not bound to plasma proteins and has a volume of distribution equal to 57.7 litres. In patients with epilepsy, gabapentin concentrations in cerebrospinal fluid (CSF) are approximately 20% of corresponding steady-state trough plasma concentrations. Gabapentin is present in the breast milk of breast-feeding women.

Biotransformation:
There is no evidence of gabapentin metabolism in humans. Gabapentin does not induce hepatic mixed function oxidase enzymes responsible for drug metabolism.
Excretion:
Gabapentin is eliminated unchanged solely by renal excretion. The elimination half-life of gabapentin is independent of dose and averages 5 to 7 hours.
In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced.
Gabapentin elimination-rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance.
Gabapentin is removed from plasma by haemodialysis. Dosage adjustment in patients with compromised renal function or undergoing haemodialysis is recommended.
Gabapentin pharmacokinetics in children were determined in 50 healthy subjects between the ages of 1 month and 12 years. In general, plasma gabapentin concentrations in children > 5 years of age are similar to those in adults when dosed on a mg/kg basis.
In a reported pharmacokinetic study in 24 healthy paediatric subjects aged between 1 month and 48 months, an approximately 30% lower exposure (AUC), lower Cmax and higher clearance per body weight have been observed in comparison to available reported data in children older than 5 years.

Linearity/Non-linearity

Gabapentin bioavailability (fraction of dose absorbed) decreases with increasing dose which imparts non-linearity to pharmacokinetic parameters which include the bioavailability parameter (F) e.g. Ae%, CL/F, Vd/F. Elimination pharmacokinetics (pharmacokinetic parameters which do not include F such as CLr and T1/2), are best described by linear pharmacokinetics. Steady state plasma gabapentin concentrations are predictable from single-dose data.
Methylcobalamin
Evidence indicates methylcobalamin is utilized more efficiently than cyanocobalamin to increase levels of one of the coenzyme forms of Vitamin B12 Experiments have demonstrated similar absorption of methylcobalamin following oral administration. The quantity of cobalamin detected following a small oral dose of methylcobalamin is similar to the amount following administration of cyanocobalamin; but significantly more cobalamin accumulates in liver tissue following administration of methylcobalamin. Human urinary excretion of methylcobalamin is about one third that of a similar dose of cyanocobalamin, indicating substantially greater tissue retention

5.3 PRECLINICAL SAFETY DATA
Not applicable

6. PHARMACEUTICAL PARTICULARS
6.1 LIST OF EXCIPIENTS
Micro crystalline cellulose
Maize starch
Methyl hydroxy benzoate
Propyl hydroxy benzoate
Povidone
Isopropyl alcohol
Magnesium stearate
Purified talc
Sodium lauryl sulphate
Sodium starch glycolate
Maize starch (additional)
Hypromellose
Ponceau lake 4R
Titanium dioxide
Purified talc
Propylene glycol
Isopropyl alcohol
Dichloromethane

6.2 INCOMPATIBILITIES:
None such data reported

6.3 SHELF-LIFE:
24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE:
Store below 30°C. Protected from light.

6.5 NATURE AND CONTENTS OF CONTAINER:
Aluminium - PVC Blister Pack
10 Tablet are blister packed with Aluminium - PVC foil; such 3 blisters are packed in one carton pack.
Pack size: 3 x 10 Tablets (i.e. 30 Tablets) in one carton box along with packing leaflet.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING:
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES: --

MARKETING AUTHORIZATION HOLDER:
GALAXY PHARMACEUTICAL LTD
P.O. Box 39107-00623, Nairobi, Kenya

MANUFACTURING SITE ADDRESS:
FREDUN PHARMACEUTICALS LTD.
14, 15, 16, Zorabian lndustrial Complex,
Vevoor, Palghar(E)-401 404.INDIA

8. MARKETING AUTHORIZATION NUMBER:
CTD8784

9. DATE OF FIRST AUTHORIZATION /RENEWAL OF THE AUTHORIZATION:
28/07/2026

10. DATE OF REVISION OF TEXT:
28/07/2026